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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,927	10/03/2003	Steven A. Gould	02-896-A	1206

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/678,927	GOULD ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT OF IDS, STATUS OF THE APPLICATION AND CLAIMS

1. The information disclosure statement (IDS) and Form PTO-1449 filed 102/09/04 are acknowledged, entered and considered. Claims 1-47 are now pending in the application.

OBJECTION TO TRADEMARK AND ITS USE

2. The use of the trademark "PolyHeme®" has been noted in this application. The trademark has not been capitalized, it should be capitalized whenever it appears and be accompanied by the generic terminology. Although, the use of trademark is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent its use in a manner, which might adversely affect their validity as trademark.

Further, the specification, which specifies the generic terminology should include, published product information sufficient to show that the generic terminology or the generic description are inherent in the article referred by the trademark. These description requirements are made because the nature and composition of articles denoted by trademark can change and affect the adequacy of the disclosure.

OBJECTIONS TO THE SPECIFICATION AND CLAIMS

3. The specification is objected on page 7, paragraph 0029, line 18 in the recitation "up to at least twenty units (10L)" and also on page 12, paragraph 0037, line 2; page 14,

paragraph 0043, line 18; and page 17, paragraph 0051, line 10 in the recitation "20 units (1000g, 10L)", respectively. According to Gould et al (one of the co-inventors of the instant invention) **1 unit = 50 gram**. Thus 20 units = 1000 gram which is 1 L. See e.g., the abstract of Gould et al (The Journal of Trauma, Injury, Infection and Clinical Care, Vol. 43, No. 2, pp. 325-332, August 1997). Similarly, Figures 1 and 2 of the instant specification discloses up to 20 units and define that **one unit** of the polymerized hemoglobin solution contains **50 g** in 0.5 L (i.e. 10 units). See e.g., paragraphs 0017 and 0018 in the instant specification as well as Figures 1 and 2. Thus, the recitation "up to at least twenty units (10L)" and "20 units (1000g, 10L)" appears to be typographical errors. It should be 20 units (1000g, 1L) because I unit = 50 g. Appropriate correction is required.

Further, claims 4, 16, 25, 32 and 42 are objected in the recitation "of at least 5L" for the same reasons discussed above in the objection of the specification. Appropriate correction is suggested.

CLAIMS REJECTION-35 U.S.C. § 102(b)

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5-9, 11, 22, 23, 26-31, 33-37, 39-41 and 43-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Gould et al (The Journal of Trauma, Injury, Infection and Clinical Care, Vol. 43, No. 2, pp. 325-332, August 1997).

The reference of Gould et al. discloses like the instantly claimed invention methods for treating mammals suffering from a life threatening level of red blood cell hemoglobin (RBC Hb) as the result of blood loss from acute trauma and urgent surgery by administering an acellular red blood cell substitute, essentially tetramer-free, crosslinked, polymerized hemoglobin solution which is free of stromal contaminants. The prior art administered up to 6 units (i.e., about 300 g) of hemoglobin solution in 20 minutes, depending on the urgency of the situation to maintain a mean circulating hemoglobin level greater than 10.0 g/dl and arterial pressure of less than 100 mm Hg due to blood loss. The prior art provides hemoglobin substitute solutions that avoid the toxicities associated with vasoconstriction, renal, hepatic and cardiac dysfunctions (See Title, abstract, experimental protocol, discussion, Figure 2 and Tables 1 and 3) as directed to claims 1-3, 5-9, 11, 22, 23, 26-31, 33-37, 39-41 and 43-46. Therefore, the reference clearly discloses methods of treating mammals including humans from massive blood loss by administering polymerized hemoglobin solutions to maintain mean circulating hemoglobin levels above 5.0 g/dl, and as such, substantially discloses the invention as claimed and anticipates claims 1-3, 5-9, 11, 22, 23, 26-31, 33-37, 39-41 and 43-46 as drafted.

CLAIMS REJECTION-35 U.S.C. § 103(a)

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gould et al (The Journal of Trauma, Injury, Infection and Clinical Care, Vol. 43, No. 2, pp. 325-332, August 1997) taken with DeWoskin et al (U.S. Patent No. 6,498,141 and Sehgal et al (Surgery, Vol. 95, No. 4, pp. 433-438, April 1984).

Gould et al. as discussed above discloses like the instantly claimed invention methods for treating mammals suffering from a life threatening level of red blood cell hemoglobin (RBC Hb) as the result of blood loss from acute trauma and urgent

surgery by administering an acellular red blood cell substitute, essentially tetramer-free, crosslinked, polymerized hemoglobin solution which is free of stromal contaminants. The prior art administered up to 6 units (i.e., about 300 g) of hemoglobin solution in 20 minutes, depending on the urgency of the situation to maintain a mean circulating hemoglobin level greater than 10.0 g/dl and arterial pressure of less than 100 mm Hg due to blood loss. The prior art provides hemoglobin substitute solutions that avoid the toxicities associated with vasoconstriction, renal, hepatic and cardiac dysfunctions.

The reference of Gould et al. differs from claims 1-47 in not teaching a) the administration of hemoglobin solution in an amount of at least 5L as claimed in claims 4, 16, 25, 32 and 42, b) the molecular weight distribution as recited in claims 10, 21, 24, 38 and 47 and c) to a method of preventing anemia, irreversible ischemia, or hypovolemic shock in a patient suffering massive blood loss as claimed in claims 12-21. With respect to the of hemoglobin solution in an amount of at least 5L as claimed in claims 4, 16, 25, 32 and 42, although, the primary reference of Gould et al clearly discloses the administration of up to 6 units which is about 300 g of hemoglobin. However, it is believed that the recitation of 5L is typographical error for the reasons discussed above under the objections to the specification and claims. Nevertheless, the secondary reference of DeWoskin et al ('141 patent) clearly teaches the administration/transfusion of an amount of a stroma-free, tetramer-free, polymerized, pyridoxylated hemoglobin solution that is non-toxic to the human patient, where the amount is up to at least about 5.0 L (See e.g., abstract, col. 4, lines 20-25). The

reference also states on col. 4, lines 43-63 that the infusion in amount up to at least about 5.0 L, does not cause vasoconstriction, renal toxicity, hemoglobinuria and other problems implicated with intravenous administration of known hemoglobin solutions containing physiologically undesirable amounts of tetrameric hemoglobin. The product also, is useful in the treatment of any disease or medical condition requiring a resuscitative fluid (i.e., trauma, specifically hemorrhagic shock). Similarly, the secondary reference of Sehgal et al teaches the transfusion of up to 900 ml (i.e. 0.9 L) of polymerization of pyridoxylated stroma free hemoglobin (poly SFH-P) to adult baboons (See e.g., abstract). Thus, in view of the secondary references teachings, and particularly in view of DeWoskin's teachings, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the administration of large volume of hemoglobin solution (i.e., up to at least about 5.0 L) into the primary reference's teachings which suggests the use of a polymerized hemoglobin solution to treat patients suffering from massive hemorrhage (i.e., bleeding) for the intended purposes of providing immediate life-sustaining therapy until adequate red blood cell hemoglobin levels (i.e., RBC Hb concentrations) can be restored.

In regard to the molecular weight distribution of claims 10, 21, 24, 38 and 47, the molecular weights are not disclosed in the primary reference; however, the claims do not define the molecular weight distribution as functional limitation, rather, the claims define the molecular weight distribution as property of hemoglobin solution. Further, the primary reference of Gould et al as well as the claimed invention has substantially

the same compound/composition (i.e., acellular red blood cell substitute). Thus, the crosslinked hemoglobin solution of the primary reference would have the same molecular weight distribution as claimed because the molecular weight is an expected property, which is a characteristic when a solution is purified from the same compound/composition. Nevertheless, the prior art of the secondary reference of DeWoskin et al ('141 patent) on the Table of col. 6 discloses polymerized hemoglobin having a molecular weight distribution of a) form about 10-24% by weight of polymerized hemoglobin of polymer having molecular weight of 128 KDa, b) form about 18-30% by weight of polymerized hemoglobin of polymer having molecular weight of 192 KDa, and c) form about 45-70% by weight of polymerized hemoglobin of polymer having molecular weight of 256 KDa, which overlaps with claimed ranges of claims 10, 21, 24, 38 and 47 (See also claims 1, 13, 14 and 26 of '141 patent). Similarly, the secondary reference of Sehgal et al discloses on page 435, right column, last paragraph and Figure 5, the molecular distribution of poly FSH-P in plasma ranging from 64 kDa to 600 kDa, which overlaps with the claimed ranges of 128 kDa to 256 kDa.

With respect to a method of preventing anemia, irreversible ischemia, or hypovolemic shock in a patient suffering from massive blood loss by administering to the patient a volume of a polymerized hemoglobin solution sufficient to maintain total hemoglobin above 5.0 g/dl and arterial pressure above 60 mm Hg. The primary reference of Gould et al. as discussed above clearly teaches the administration of polymerized hemoglobin solution (poly S FH-P) as blood substituent in treating acute

blood loss (which may encompass anemia, ischemia and hypovolemic shock) that occurs after acute trauma and urgent surgery. Further, the secondary reference of Sehgal et al. on page 437, left column, concludes by stating that our current data suggest that poly SFH-P will be effective as an acellular oxygen carrier. Its efficacy will have to be confirmed in a variety of animal models that may include a total exchange transfusion, resuscitation from normovolemic anemia, and resuscitation from hemorrhagic shock. Thus, clearly suggesting that the claimed composition/compound can be applied to any kind of massive blood loss including anemia, ischemia and hypovolemic shock.

Therefore, in view of this and in view of the combined teachings of the prior art at the time the invention was made, one of ordinary skill in the art would have been motivated to employ methods for treating mammals suffering from a life threatening level of red blood cell hemoglobin as the result of blood loss from acute trauma and urgent surgery by administering an acellular red blood cell substitute, essentially tetramer-free, crosslinked, polymerized hemoglobin solution which is free of stromal contaminants. Thus, the combined teachings of the prior art makes *prima facie* obvious methods of administering a polymerized hemoglobin solution in an amount of at least 5L having various molecular weight distributions for treating massive bleeding in mammals including humans suffering from massive hemorrhage (i.e., anemia, irreversible ischemia, or hypovolemic shock) having total hemoglobin less than 7 g/dl, wherein said administration result in restoring adequate life-sustaining red blood cell hemosolution levels above 5.0 g/dl and arterial pressure above 60 mm Hg, absent of

sufficient objective factual evidence or unexpected results to the contrary.

CITATION OF RELEVANT PRIOR ART

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Sehgal et al (U.S. Patent No. 6,323,320) disclose an acellular red blood cell substitute comprising an essentially tetramer-free, substantially stroma-free, crosslinked, polymerized, pyridoxylated hemoglobin and a nontoxic, pharmaceutically acceptable carrier, its use, and a process for preparing said acellular red blood cell substitute thereof.

CONCLUSION AND FUTURE CORRESPONDANCE

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, CAMPELL BRUCE can be reached on (571) 272 0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JON WEBER
SUPERVISORY PATENT EXAMINER

Mohamed/AAM
March 3, 2006